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(54) **UTILISATION D'ADDITIFS AJOUTES A DES AGENTS CONTRASTANTS POUR AMELIORER L'IMAGERIE**

(54) **USE OF ADDITIVES IN CONTRAST MEDIA TO IMPROVE IMAGING**

(57) L'invention concerne l'utilisation de dérivés de prostacycline, ainsi que celle d'urée pour améliorer l'imagerie dans les diagnostics effectués par radiographie, ultrasons, résonance magnétique ou résonance magnétique nucléaire.

(57) The invention concerns the use of prostacycline derivatives and the use of urea in order to improve imaging in X-ray, ultrasound, nuclear or MRI diagnostics.

Use of Additives in Contrast Media to Improve Imaging

Abstract

The invention relates to the use of prostacyclin derivatives as well as the use of urea to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

Use of Additives in Contrast Media to Improve Imaging

The invention relates to the use of prostacyclins and urea as additives in contrast media to improve imaging.

Description

Contrast media are indispensable additives in diagnostic radiology; magnetic resonance, nuclear or ultrasonic diagnosis for general improvement of imaging, for more specific displaying of individual organs or tissues, or for visualization of "dynamic" processes or pathological conditions. Summary visualizations are described in the literature.

In diagnostic radiology, imaging is based on the different levels of absorption of the irradiated tissue or on absorption of the x-ray radiation by the contrast medium. All parenterally administered x-ray contrast media use iodine as a ray-absorbing element, and the substances currently available contain either three or six iodine atoms per molecule to achieve as high a contrast as possible. All commercially available x-ray contrast media are derivatives of triiodobenzene. In this case, these are either monomeric compounds with three iodine atoms or dimeric derivatives with six iodine atoms, which have two triiodobenzene derivatives that are connected via a bridge. Additional substituents increase hydrophilia and improve compatibility.

After intravenous or intraarterial injection of the x-ray contrast media, these compounds are dispersed very quickly into the extracellular space and are then excreted via the kidneys by glomerular filtration.

The search for contrast media for diagnostic radiology began immediately after the discovery of x rays by W. C. Röntgen in the year 1895. The goals or desired properties for these contrast media have not changed significantly since. Well-tolerated substances with high ray-absorbing potential are sought. With the introduction of three or six iodine atoms per molecule, however, a limit in ray absorption was obviously reached which at this time cannot be exceeded despite the most intensive efforts.

As an alternative, attempts have therefore been made by various research groups to improve the imaging of blood vessels in particular by adding pharmacologically active substances to the triiodine or hexaiodine compounds. In this case, papaverine was studied the most intensively. It was shown that by adding papaverine to x-ray contrast media, the imaging of vessels can be improved or that the combination of x-ray contrast media with papaverine can be used even for differential diagnosis of myocardial insufficient blood supply (Cheirif et al. J. Am. Coll. Cardiol. 11: 735-743, [1988]; Hodgson and Williams, Am. Heart J. 114: 704-10 [1987]). It turned out very quickly, however, that precipitation can occur in mixing the contrast medium with papaverine, leading to thrombosis and even death (Irving and Burbridge, Radiology 173: 91-2 [1989]; Shah and Gerlock, Radiology 162: 619-20 [1987]; Pallan et al., Proc. West.

Pharmacol. Soc. 34: 315-7 [1991]; Burbridge, Radiology 189: 287 [1993]; Delcour, Am. J. Roentgenol. 147: 1096 [1986]; McGill et al., Radiology 166: 577-8 [1988]; Pilla et al., Am. J. Roentgenol. 146: 1300-1 [1986]). These incompatibilities, which were initially reported only for ionic contrast media such as amidotrizoate or ioxaglat, were, however, also later found for nonionic compounds such as iopamidol (Pallan et al., Radiology 187: 257-9 [1993]), so that the addition of papaverine was greatly restricted.

In the search for alternatives, other vasodilators, such as dipyramidole and tolazoline, were investigated with regard to their effectiveness. Improvements in imaging were thus achieved, especially in the heart (Johnston et al., J. Nucl. Med. 28: 871-7 [1987]; Burgener and Gutierrez; Invest. Radiol. 20: 399-402 [1985]). Solubility problems, however, were again very soon reported here as well (Zagoria et al., Invest. Radiol. 22: 513-4 [1987]).

It is therefore very desirable to find other well-tolerated additives that are not affected by miscibility problems in contrast media that can improve imaging.

The object is therefore to make available such additives in contrast media.

This object was achieved by this invention.

It has now been found that, surprisingly enough, the addition of prostaglandin derivatives to contrast media effectively ensures that the imaging in the vessels, but also in

the kidneys and the urinary passages is considerably improved and that urea also satisfies this claim.

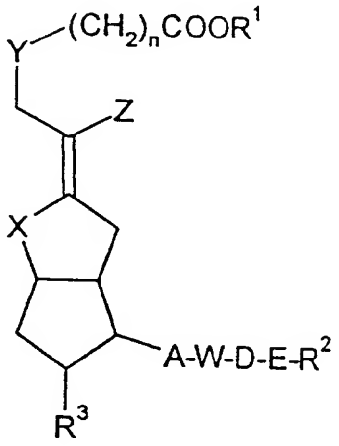
Contrast media in this sense are x-ray, MRI or ultrasonic contrast media and nuclear diagnostic agents.

This invention therefore relates to the object that is characterized in the claims, namely the use of prostaglandin derivatives as well as of ureas to improve imaging of contrast media in diagnostic radiology; MRI, ultrasonic or nuclear diagnosis. Cyclodextrin clathrates of prostaglandins are also to be defined as prostaglandin derivatives.

As examples of prostaglandin derivatives, those that are suitable for this use can be mentioned by way of example: Ataprost (INN), beraprost (INN), ciprostene (INN), CS 570 (INN), FCE 22509 (INN), naxaprostene (INN), RS 93427 (INN), SC 39902 (INN), taprostene (INN), 5-[(E)-(1S,5S,6S,7R)-7-hydroxy-6-[(3S,4S)]-3-hydroxy-4-methyl-1,6-nona-diinyl]-bicyclo[3.3.0]-oct-3-ylidene]-pentanoic acid and 5-[(E)-(1S,5S,6S,7R)-7-hydroxy-6-(3S,4S)-3-hydroxy-4-methyl-1,6-nonadiinyl]-bicyclo[3.3.0]-oct-3-ylidene]-5-fluoro-3-oxapentanoic acid.

The invention preferably relates to the use of urea and/or

one or more prostacyclin derivatives of general formula (I)



(I)

in which

R^1 stands for hydrogen or a C_1-C_8 alkyl radical,

n stands for numbers 0 to 3,

X,Y, independently of one another, stand for a $-CH_2$ group or an oxygen atom,

Z stands for hydrogen, fluorine, or CN,

A stands for a trans -CH=CH or a -C≡C group,

W stands for a hydroxymethyl group that is free or functionally modified at the hydroxy group, whereby the hydroxy group can be in α- or ß-position,

D stands for a straight-chain or branched C_1-C_5 alkylene group,

E stands for a -C≡C group,

R^2 stands for a C_1-C_2 alkyl group,

R^3 stands for a free or functionally modified hydroxy group,

as well as their cyclodextrin clathrates,
and -- if R^1 means hydrogen -- their salts with physiologically compatible bases,
to improve imaging with the use of x-ray, ultrasonic, nuclear or NMR contrast media.

This invention especially preferably relates to the use of the prostacyclin derivatives iloprost, iloprost-clathrate, cicaprost, cicaprost-clathrate, eptaloprost or eptaloprost-clathrate.

The alkyl groups in R^1 are straight-chain or branched-chain alkyl groups with 1 to 8 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl. Alkyl groups R^1 can optionally be substituted by fluorine, chlorine, bromine or iodine atoms; methoxy, ethoxy, phenyl or (C_1-C_2) dialkylamino groups, such as dimethylamine or diethylamine. Preferred alkyl groups R^1 are methyl, ethyl and dimethylaminopropyl.

R^2 can stand for a methyl or an ethyl radical.

The hydroxy groups in R^3 and W can be present as free hydroxy groups, whereby the hydroxy group in W is preferably in α-position, or can be functionally modified, for example, by etherification or esterification. Free hydroxy groups are preferred.

The radicals that are known to one skilled in the art are considered as ether or acyl radicals. Preferred are easily cleavable ether radicals, such as, for example, tetrahydropyranyl, tetrahydrofuranyl, α-ethoxyethyl,

trimethylsilyl, dimethyl-tert-butylsilyl, diphenyl-tert-butylsilyl, or tribenzylsilyl.

As acyl radicals, there can be mentioned, for example, acetyl, propionyl, butyryl or benzoyl.

As alkylene group D, straight-chain or branched saturated alkyl groups with 1 to 5 C atoms are considered, for example, methylene, ethylene, 1- propylene, 2-propylene, ethylethylene, trimethylene, tetramethylene, pentamethylene, 1-methyldimethylene, 1-methyltrimethylene, and 1-methyltetramethylene.

For ionic bonding with free acids (R^1 = H), inorganic and organic bases are suitable, as they are known to one skilled in the art for the formation of physiologically compatible salts. For example, there can be mentioned: alkali hydroxides such as lithium, sodium or potassium hydroxide; alkaline-earth hydroxides, such as calcium hydroxide, ammonia; amines such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, tris(hydroxymethyl)methylamine, glucosamine, lysine, ornithine and arginine.

The clathrates with α-, ß- or γ-cyclodextrin are obtained analogously to the instructions of WO 87/05 294. ß-Cyclodextrin clathrates are preferred.

The production of compounds of formula I is described in detail in EP 2 234 B1 and EP 11 591 B1.

In EP 11 591 B1, the following pharmacological properties for prostacyclin derivatives of formula I are described:

Lowering of peripheral, arterial, and coronary vascular resistance, inhibition of platelet aggregation and dissolution of platelet thrombi, myocardial cytoprotection and thus lowering of systemic blood pressure without reducing cardiac output and coronary blood circulation at the same time; treatment of stroke, prophylaxis and treatment of coronary thrombosis, myocardial infarction, peripheral arterial diseases, arteriosclerosis, and thrombosis, treatment of shock, inhibition of stomach acid secretion and cytoprotection of the mucous membrane of the stomach and intestines; anti-allergic properties, lowering of pulmonary vascular resistance and of pulmonary blood pressure, use to replace heparin or as an adjuvant in dialysis or hemofiltration, preservation of dried blood plasma, especially of dried blood platelets, inhibition of labor pains, treatment of gestational toxicosis, improvement of cerebral blood circulation, etc. In addition, the new prostaglandin analogs have antiproliferative properties.

In EP 86 404 B1, the use of carbacyclins for prophylaxis and treatment of ischemic attacks of the central nervous system, for cytoprotection in the liver and the pancreas, as well as the combination with ß-blockers or diuretics, is described. From DE 34 27 797 C2, the cytoprotection of the kidneys as well as the suitability of the prostacyclin derivatives of formula I for the treatment of organs to be transplanted is known. In DE 35 26 362 A1, the combination of the prostacyclin derivatives of formula I with thromboxane antagonists for use in the case of thrombotic or thrombo-embolic syndromes is described.

From DE 35 44 663 A1, the combination of prostacyclin derivatives of formula I with fibrinolytic agents to prevent rethromboses after a thrombosis is known.

In DE 36 08 088, the clathrates of the carbacyclin derivatives of formula I are described. From DE 36 31 169 A1, the topical form of administration, in addition to the forms of administration described in EP 11 591 B1, is known.

In DE 41 35 193 C1, the use of the above-mentioned compounds as additives to avoid or to treat microcirculation disorders -- thus the terminal vascular system that cannot be imaged (submacroscopic vessels) -- after the administration of x-ray, ultrasonic or MRI contrast media is described.

The use of the prostacyclin derivatives that is claimed within the scope of this invention is not mentioned or suggested in any of the above laid-open specifications or patents or in the other literature.

Very surprisingly, studies on the animal model have shown that the above-mentioned compounds can be used successfully in improving imaging by x-ray, ultrasonic, nuclear or MRI contrast media. The concentration range of the prostacyclin derivatives added to the contrast media is preferably approximately 0.1-100 ng/ml. In this concentration range, an improvement in imaging also occurs even without administration of contrast media, especially in MRI diagnosis and angiography.

The use of urea to improve imaging is not described in any publication. The sole study that was reported in the literature relates to the change in diuresis after administration of sodium

iodide by the addition of urea (A. Roseno, Klin. Wochenschr. 25: 1165-70 [1929]). This work was aimed primarily at the faster elimination and thus quicker detoxification of sodium iodide, which is highly toxic in comparison with modern-day x-ray contrast media.

It has now been found that the addition of urea to modern-day x-ray contrast media is, surprisingly enough, able to considerably improve imaging in the urogram, although urea leads to strong osmodiuresis and thus to dilution of the eliminated contrast medium. The less concentrated contrast medium in the urine should actually produce poorer image quality. Corresponding disadvantageous findings are obtained after the addition of mannitol to a nonionic contrast medium (I. Lovelt et al., in Recent Developments in Nonionic Contrast Media, V. Taenzer, S. Wende: Fortschr. Röntgenstr. Suppl. 128: 105-7 [1989]). The range of concentration of the urea added to the contrast media is preferably approximately 10-150 mg/ml. In this range of concentration, an improvement in imaging also occurs even without administration of contrast media, especially in MRI diagnosis and angiography.

Examples

The following examples are used for a more detailed explanation of the object of the invention without intending to be limited to this object.

1. Addition of iloprost to ultravist: visualization of vessels

A rabbit with a body weight of about 3 kg received an injection of nonionic low-osmolal x-ray contrast medium Ultravist(R)-300 (active ingredient: iopromide (INN)) in the common carotid. The dose was 2 ml/kg, and the rate of injection was 1-1.5 ml/sec. Immediately thereafter an angiogram was taken (Fig. 1).

After a resting phase, the test was repeated, whereby this time 10 ng/ml of iloprost was added to the contrast medium. The result is presented in Fig. 2.

After another resting phase, the test was conducted once more. This time, however, the injection again consisted of Ultravist(R)-300 without addition of iloprost.

Result:

The addition of 10 ng/ml of iloprost to Ultravist(R)-300 improved the angiogram to an extraordinary extent. A new injection of Ultravist(R)-300 again showed the original -- less well defined -- angiogram.

2. Addition of iloprost to ultravist: use in urography

A rabbit with a body weight of about 3 kg received an intravenous injection of nonionic low osmolal x-ray contrast medium Ultravist(R)-370 (active ingredient: iopromide (INN)). The dose was 2 ml/kg, and the rate of injection was 1-1.5 ml/sec. Immediately thereafter a urogram was taken (Fig. 3).

After a resting phase, the test was repeated, whereby this time 10 ng/ml of iloprost (INN) was added to the contrast medium. The result is presented in Fig. 4.

After another resting phase, the test was conducted once more. This time, however, the injection again consisted of Ultravist(R)-370 without addition of iloprost.

Result:

The addition of 10 ng/ml of iloprost to Ultravist(R)-370 clearly improved the urogram.

3. Addition of urea to isovist: use in urography

The study was designed as a block test. In the first block, in each case 3 animals were treated with Isovist(R)-280 (active ingredient: iotrolan (INN)) and 3 animals with Isovist(R)-280 + 52 mg of urea/ml. In the second block -- 3 days later -- the corresponding other formulation was administered to the animals.

Result:

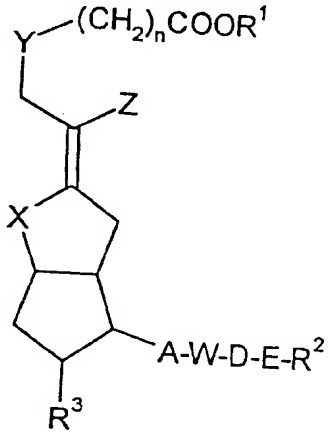
The addition of 52 mg of urea to one ml each of Isovist(R)-280 clearly improved the urogram (Figs. 5 and 6); in particular, the renal calices are better contrasted.

Claims

1. Use of a prostaglandin derivative to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

2. Use of a prostaglandin derivative in combination with a contrast medium to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

3. Use of the prostacyclin derivatives of general formula I



(I)

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R^2 stands for a C_1-C_2 alkyl group,

R^3 stands for a free or functionally modified hydroxy group,

as well as their cyclodextrin clathrates,

and -- if R^1 means hydrogen -- their salts with physiologically compatible bases,

to improve the imaging with the use of x-ray, ultrasonic, nuclear or MRI contrast media according to claim 1 or 2.

4. Use of iloprost, cicaprost, eptaloprost or a cyclodextrin clathrate of these compounds according to claim 1 or 2.

5. Use of 5-[(E)-(1S,5S,6S,7R)-7-hydroxy-6-[(3S,4S)]-3-hydroxy-4-methyl-1,6-nona-diinyl]-bicyclo[3.3.0]-oct-3-ylidene]-pentanoic acid, 5-[(E)-(1S,5S,6S,7R)-7-hydroxy-6-[3S,4S]-3-hydroxy-4-methyl-1,6-nona-diinyl]-bicyclo[3.3.0]-oct-3-ylidene]-5-fluoro-3-oxapentanoic acid or a cyclodextrin clathrate of these compounds according to claim 1 or 2.

6. Use of ataprost (INN), beraprost (INN), ciprostene (INN), CS 570 (INN), FCE 22509 (INN), naxaprostene (INN), RS 93427 (INN), SC 39902 (INN), taprostene (INN), or a cyclodextrin clathrate of these compounds according to claim 1 or 2.

7. Use of urea to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

8. Use of urea in combination with a contrast medium to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

9. Use of a prostacyclin derivative according to claim 1, 2 or 3 together with urea to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis.

10. Use of a prostacyclin derivative according to claim 1, 2 or 3 together with urea to improve imaging in diagnostic radiology; ultrasonic, nuclear or MRI diagnosis in combination with a contrast medium.

Fig. 1

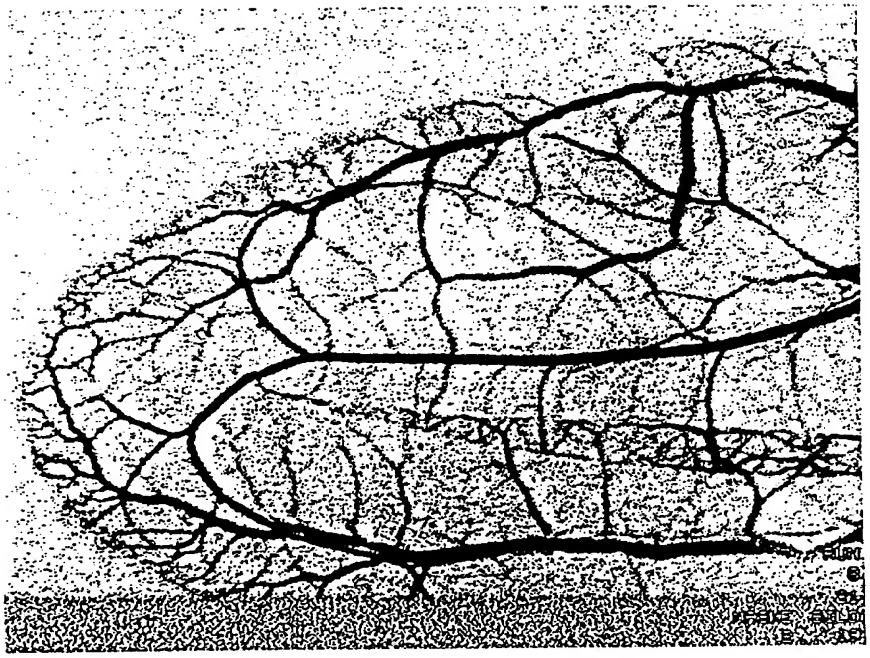

Fig. 2

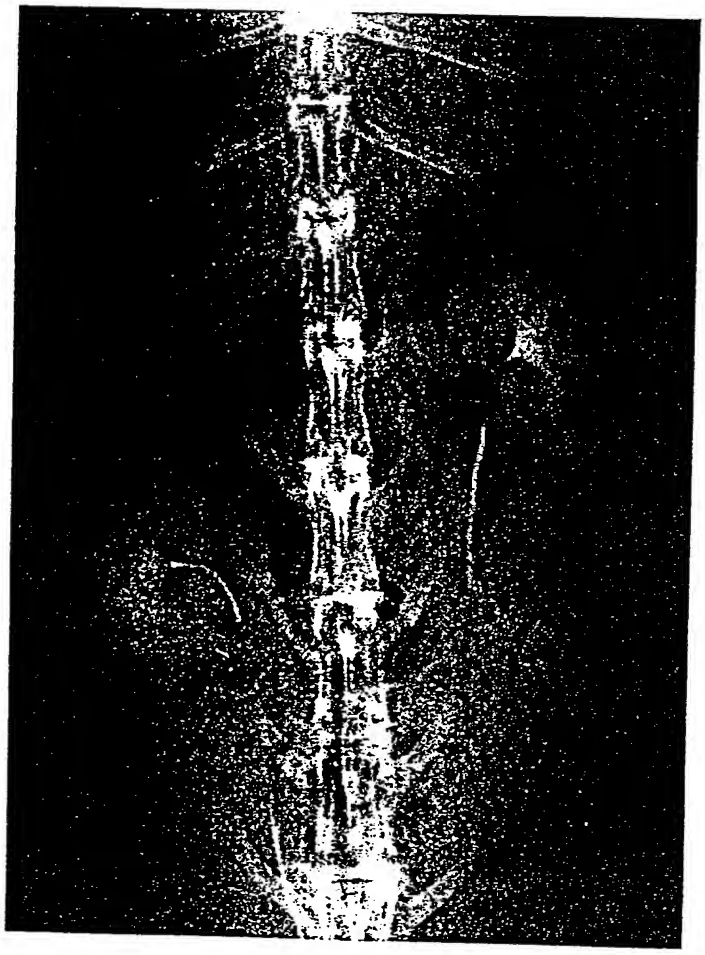

Fig. 3

Fig. 4

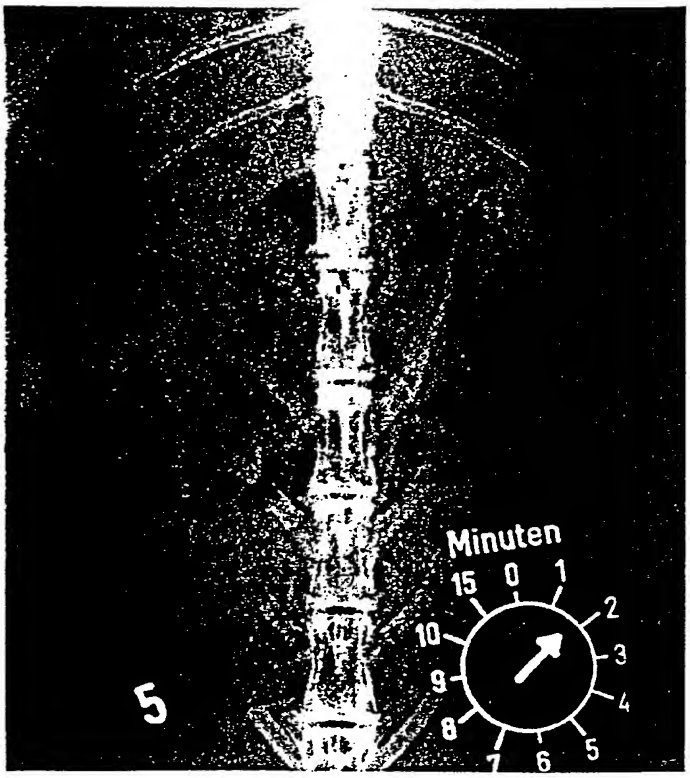

Fig. 5

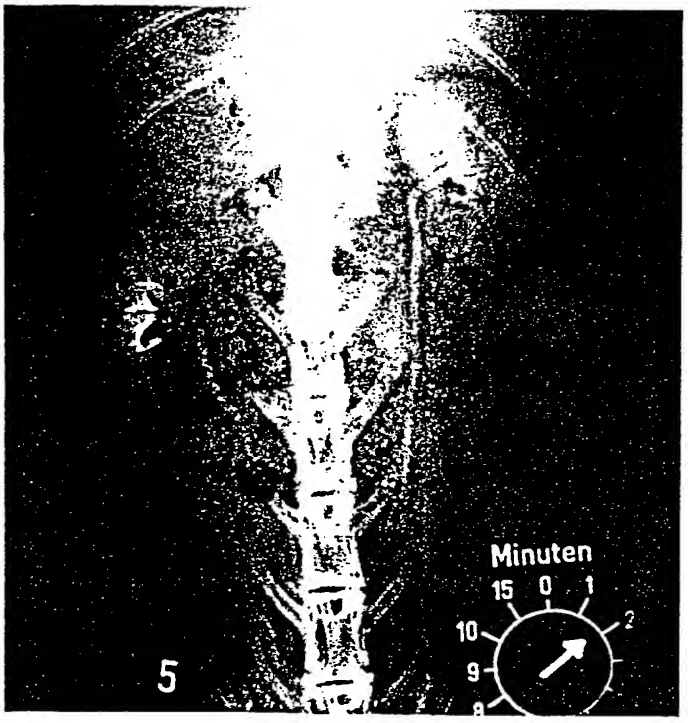

Fig. 6